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09/012,846	01/23/1998	MARC F. CHARETTE	CIBT-P01-510	2619

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EXAMINER	
TURNER, SHARON L	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 05/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/012,846	CHARETTE, MARC F.	
	Examiner	Art Unit	
	Sharon L. Turner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-36,46-48 and 52-63* is/are pending in the application.

4a) Of the above claim(s) *33-36 and 60-63* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-32,46-48 and 52-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *28-36,46-48 and 52-63* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1-30-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Response to Amendment

1. The amendment filed 2-25-04 has been entered into the record and has been fully considered.

2. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

3. As a result of Applicants amendment, all rejections not reiterated herein have been withdrawn by the examiner.

4. Claims 28-36, 46-48 and 52-63 are pending.

Election/Restriction

5. Claims 33-36 and 60-63, drawn to the extent of BMP-2, BMP-5, BMP-6 and 60A stand withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected species, there being no allowable generic or linking claim. Election was made without traverse in Paper No. 18.

Specification

6. The attempt to incorporate subject matter into this application by reference to WO94/03600 is improper because the particular subject matter incorporated by reference at p. 29 of the specification does not apparently correlate to the subject matter now disclosed as newly amended 5-8-03 between the first and second paragraphs on p. 29. Applicant's originally filed specification does not apparently support the specific incorporations as notated within Figure 1 of the WO94/03600 publication and to various other recitations of OP-1 sequences, N-terminal signal sequences, Pro regions, particular domains, and preferred generic recitations as to the forms of OP-1. The

recitations do not apparently correlate and do not appear to be direct incorporations by reference.

Mere reference to another application, patent, or publication is not an incorporation of anything therein into the application containing such reference for the purpose of the disclosure required by 35 U.S.C. 112, first paragraph. In re de Seversky, 474 F.2d 671, 177 USPQ 144 (CCPA 1973). In addition to other requirements for an application, the referencing application should include an identification of the referenced patent, application, or publication. Particular attention should be directed to specific portions of the referenced document where the subject matter being incorporated may be found. See MPEP § 608.01(p) for Office policy regarding incorporation by reference. The specific material incorporated does not apparently correlate from instant specification to the published WO document.

7. The amendment filed 5-8-03 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: Amendment to p. 29 between the first and second paragraphs submitted 5-8-03. Support is not directly found for the new recitations as incorporated by reference within the original specification and as in WO 94/03600.

Claim Rejections - 35 USC 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner

> and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 28-32, 46-48 and 52-59 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The claims as amended are directed to a method for enhancing formation and development of dendrites and synapses in hippocampal neurons comprising contacting said neurons with a morphogen comprising a conserved C-terminal seven-cysteine skeleton at least about either 60% (claim 28) or 70% (claim 52) homologous to residues 330-431 of human OP-1 (SEQ ID NO:2), or comprising residues 30-292, 330-431, 48-292, 293-329, 293-431 and 30-431of human OP-1 (SEQ ID NO:2), wherein said morphogen induces dendrite outgrowth in said hippocampal neuron.

Support is not found for the combination of activities and isoforms of OP-1 as disclosed in the original specification and thus the recitations constitute new matter absent evidence for their support and combination. Applicant is required to cancel the new matter in the reply to this Office Action.

10. Claims 28-32, 46-48 and 52-59 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification describes a polypeptide sequence consisting of SEQ ID NO:2, which is shown to have the following activities: quicker induction of mature dendritic arbor at 3 days in vitro as compared to 7-14 days in vitro and increased numbers of synapses, see in particular p. 61 of the specification. However, the claims as written include polypeptides comprising various fragments and homologues, and encompass polypeptides that vary substantially in length and also in amino acid composition. The instant disclosure of a single polypeptide, that of SEQ ID NO:2 with the instantly disclosed specific activities, does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), which states:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention". Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1980) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious,"

and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d 1565, 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id at 1170, 25 USPQ2d at 1606."

A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. The instant specification discloses, however, a single isolated polypeptide sequence, SEQ ID NO: 2, and no other amino acid sequences that are shown to exhibit the same activities in growth of dendritic arbor or increased synapse formation as disclosed for SEQ ID NO: 2. Similarly, no partial sequences of SEQ ID NO:2 are shown to exhibit dendritic outgrowth or synapse formation as shown for SEQ ID NO:2.

Instead the specification appears to assert such activities to 60% to 70% homologous sequences based solely on homology considerations. While morphogens

have been shown to exhibit similar functions in bone growth, no other morphogenic molecules within the scope of the claims has been shown to exhibit similar activities in mediating growth of dendritic arbor or increased synapse formation. Receptor function, cannot be reliably predicted from protein sequence homology. For example, Transforming Growth Factor (TGF-beta) Family OP-1 induces metanephrongenesis whereas closely related TGF-beta family members-BMP-2 and TGF-beta1-have no effect on metanephrogenesis under identical conditions (Vukicevic et al., 1996, PNAS USA 93:9021-9026). Platelet-derived Growth Factor (PDGF) Family VEGF, a member of the PDGF family, is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells while PDGF is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (Tischer et al., U.S. Patent 5,194,596, column 2, line 46 to column 3, line 2). Finally, vertebrate growth hormone of 198 amino acids becomes an antagonist (inhibitor of growth) when a single amino acid is changed (Kopchick et al, U.S. Patent No. 5,350,836). Even 99% homology does allow predictability in this instance. Given the unpredictability of homology comparisons, and the fact that the specification fails to provide objective evidence that the additional sequences are indeed species of the claimed genus it cannot be established that a representative number of species have been disclosed to support the genus claim. No activity is set forth for the additional sequences. The specification further sets forth a proposed consensus sequence for the genus, yet there is no correlation or nexus provided between possession of this structural feature and the encompassed functional features of SEQ ID NO: 2 such that it is clearly conveyed that possession of any polypeptide

having this structural region in common would possess these functional features. Further, even if the proposed consensus sequence were definitive of a genus with a specified function, the instantly claimed genus is not so limited and the prior art does not provide compensatory structural or correlative teachings to enable one of skill to identify the molecules encompassed. Thus, the claimed invention lacks adequate written description support.

11. Claims 28-32, 46-48 and 52-59 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for accelerated dendritic outgrowth of hippocampal neurons in culture in the presence of OP-1 and for increased synapse formation as disclosed at p. 61, lines 1-7, does not reasonably provide enablement for these activities in the breadth of molecules generically claimed, in particular for the alternative morphogens recited, including portions of SEQ ID NO:2, and in 60-70% identical sequences to residues 330-431 of SEQ ID NO:2 in enhancing the formation and development of dendrites and synapses in hippocampal cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specifications disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without undue experimentation. The factors relevant to this discussion include the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims.

The claims as amended are directed to a method for enhancing formation and development of dendrites and synapses in hippocampal neurons comprising contacting said neurons with a morphogen comprising a conserved C-terminal seven-cysteine skeleton at least about either 60% (claim 28) or 70% (claim 52) homologous to residues 330-431 of human OP-1 (SEQ ID NO:2), or comprising residues 30-292, 330-431, 48-292, 293-329, 293-431 and 30-431of human OP-1 (SEQ ID NO:2), wherein said morphogen induces dendrite outgrowth in said hippocampal neuron.

The specification does not enable the broad scope of the claims which encompasses a multitude of analogs or equivalents because the specification does not teach which residues can or should be modified such that requisite functionality is maintained, note utility rejection above. The specification provides essentially no guidance as to which of the essentially infinite possible choices is likely to be successful in any particular use and the skilled artisan would not expect functional conservation amongst homologous sequences. Thus, applicants have not provided sufficient guidance to enable one skilled in the art to make and use the claimed derivatives in a manner reasonably correlated with the scope of the claims.

Receptor function, cannot be reliably predicted from protein sequence homology. For example, Transforming Growth Factor (TGF-beta) Family OP-1 induces metanephrongenesis whereas closely related TGF-beta family members-BMP-2 and TGF-beta1-have no effect on metanephrogenesis under identical conditions (Vukicevic et al., 1996, PNAS USA 93:9021-9026). Platelet-derived Growth Factor (PDGF) Family VEGF, a member of the PDGF family, is mitogenic for vascular endothelial cells but not

for vascular smooth muscle cells while PDGF is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (Tischer et al., U.S. Patent 5,194,596, column 2, line 46 to column 3, line 2). Finally, vertebrate growth hormone of 198 amino acids becomes an antagonist (inhibitor of growth) when a single amino acid is changed (Kopchick et al, U.S. Patent No. 5,350,836). Even 99% homology does allow predictability in this instance.

Instant specification provides only that SEQ ID NO:2 is active for accelerated dendritic outgrowth of hippocampal neurons in culture in the presence of OP-1 and for increased synapse formation as disclosed at p. 61, lines 1-7. Given the unpredictability of homology comparisons, and the fact that the specification fails to provide objective evidence that any additional sequences are indeed species of the claimed genus it cannot be established that a representative number of species have been disclosed to support the genus claim. Thus, the skilled artisan cannot make and use the claimed invention without further undue experimentation.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986).

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that

form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 28-32, 46-48 and 52-59 are rejected under 35 U.S.C. 102(b) as being anticipated by Withers et al. (1996), "Receptivity of Osteogenic Protein-I (OP-1) - Induced Dendrites to Axonal Innervation," Society for Neuroscience meeting abstract 768.8, page 1957.

Withers et al., teach OP-1 induced dendritic outgrowth of cultured hippocampal cells. In addition, the increased dendritic arbor is noted to provide for increased numbers of synaptic contacts. In particular, synapsin positive aggregates surrounding OP-1 induced dendrites indicated early stages of synapse formation. Thus the reference teachings anticipate the claimed invention.

14. Claims 28-32, 46-48 and 52-59 are rejected under 35 U.S.C. 102(b) as being anticipated by Reuger et al., WO9403200, 17 February 1994 as evidenced by Withers et al. (1996), "Receptivity of Osteogenic Protein-I (OP-1) - Induced Dendrites to Axonal Innervation," Society for Neuroscience meeting abstract 768.8, page 1957.

Reuger et al., teach morphogen-induced nerve regeneration and repair of damaged neurons and neuronal pathways, see in particular abstract. The subject morphogen includes human and mouse species of OP-1, disclosed as SEQ ID Nos:5 and 6 which share identity with instant SEQ ID NO:2. Reuger et al., teaches OP-1 enhancement of neuronal cell survival, see in particular Example 3, p. 79-81,

redifferentiation which includes neuronal cell outgrowth, see in particular Figure 1B, protection from chemical trauma, see in particular Example 5, p. 84-85, nerve-gap repair, see in particular p. 90-93, alleviation of immune response-mediated damage, Example 10, p. 97-99 and repair of neural pathways, see in particular claims 32-33. As the reference teachings of Reuger comprise repairing damaged neurons with OP-1 wherein the treatment comprises contacting neural cells with OP-1 and repairing damaged cells and pathways, the reference teachings and treatment inherently provide for dendritic outgrowth and synapse formation of the claimed hippocampal neurons as evidenced via Withers et al., 1996 which teach such activities as a result of contacting hippocampal neurons with OP-1. In particular, the treatment of Reuger includes delivery of OP-1 to hippocampal neurons to stimulate neural regeneration, see in particular p. 100. As neural regeneration is recognized to provide for the recovery of dendritic and axonal projections and to establish synapses, the reference teachings anticipate the claimed invention. It is also noted that the Reuger invention is specifically recognized for the treatment of Alzheimer's Disease where hippocampal cells are recognized to be affected by neuronal degeneration. Reuger clearly teaches that OP-1 administration is effective to stimulate CNS regeneration as disclosed for example in Example 3 and Example 7. Further, it is noted that all that is required to achieve the elements recited in the preamble are "contacting said cells with a morphogen as recited, i.e., comprising SEQ ID NO:2 or a portion of SEQ ID NO:2. Reuger teaches contacting hippocampal cells with OP-1 in particular at p. 100 and additionally results in such contact as achieved by both in vitro and in vivo administration. Thus, the Reuger

teachings are necessarily anticipatory as the methods of contacting are the same. Therefore, the Reuger teachings anticipate the claimed invention.

15. Claims 28-32, 46-48 and 52-59 are rejected under 35 U.S.C. 102(b) as being anticipated by Wang et al., WO9505846, 2 March 1995 as evidenced by Withers et al. (1996), "Receptivity of Osteogenic Protein-I (OP-1) - Induced Dendrites to Axonal Innervation," Society for Neuroscience meeting abstract 768.8, page 1957.

Wang et al., teach neural regeneration, growth and repair of damaged neural tissue using the morphogen BMP-7 which is identical to OP-1 of SEQ ID NO:2 as referenced in US 5,141,905, see in particular abstract. The method of treatment comprises contacting the neural cells with the BMP-7(OP-1) for example as claimed in claim 13-14 and 21 and provides treatment of damaged neural tissue. The treatment is specifically anticipated for the treatment of Alzheimer's as disclosed at p. 5, lines 5-14, in particular. Alzheimer's is a disease readily recognized in the art to be associated with degeneration of hippocampal neurons and thus treatment with OP-1 would be recognized for neural regeneration in hippocampal tissue. While the reference is silent that such contact results in the formation of dendrites and synapses, such is evidenced via Withers et al., 1996 as noted above. All that is required to achieve the elements recited in the preamble are "contacting said (hippocampal) cells with a morphogen as recited, i.e., comprising SEQ ID NO:2 or to peptides comprising particular portions of SEQ ID NO:2. Wang et al., teaches contacting neural cells including at the site of said defect or damage such as in hippocampal cells with BMP-7, see in particular claims 8, 13 and 21. The administration may also be intravenously, for example, p. 8, lines 3-8

and thus results in such contact achieved by in vivo administration. The Wang teachings are necessarily anticipatory as the methods of contacting are the same. Therefore, the Wang teachings anticipate the claimed invention and provide for dendritic outgrowth and synapse formation in hippocampal cells as evidenced by Withers et al., 1996 as is instantly claimed. Thus, the reference teachings anticipate the claimed invention.

Status of Claims

16. No claims are allowed.

Conclusion

17. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (571) 272-0894. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached at (571) 272-0887.

Sharon L. Turner, Ph.D.
May 14, 2004